

## **Amendments to the Claims**

This listing of claims will replace all prior versions, and listings, of claims in the application:

### **Listing of Claims**

Claim 1 (withdrawn): A method of increasing efficacy of an anti-tumor agent comprising co-administering to a patient suffering from a multidrug resistant cancer:

(a) a dose of the anti-tumor agent, wherein the anti-tumor agent is a substrate of an ABC drug transporter, and

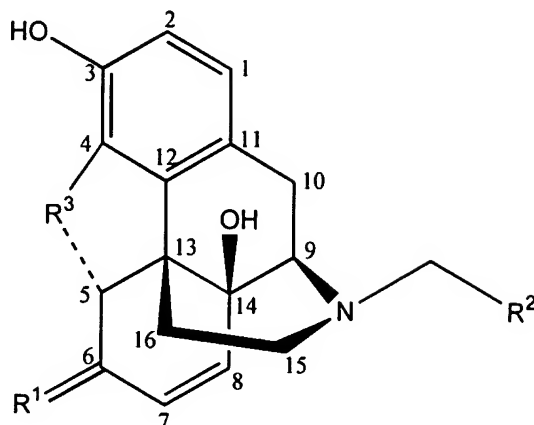
(b) a dose of an opioid inhibitor of the ABC drug transporter,

wherein the dose of the opioid inhibitor of the ABC drug transporter is sufficient to reduce efflux of the anti-tumor agent from a cancer cell and wherein the co-administration of the anti-tumor agent and the inhibitor is sufficient to inhibit growth of the cancer.

Claim 2 (withdrawn): The method of claim 1, wherein the anti-tumor agent is selected from the group consisting of Alkylating Agents, Antimetabolites, Vinca alkaloids, taxanes, epipodophyllotoxins, Anthracyclines, Antiproliferative agents, Tubulin Binding agents, Eneidyne, anthracededione, substituted urea, methylhydrazine derivatives, the Pteridine family of drugs, Taxanes, , Dolastatins, Topoisomerase inhibitors, Mytansinoids, and Platinum coordination complexes.

Claim 3 (withdrawn): The method of claim 1, wherein the dose of anti-tumor agent is a sub-therapeutic dose.

Claim 4 (withdrawn): The method of claim 1, wherein the opioid inhibitor of the ABC drug transporter is a compound of the formula:



wherein R<sup>1</sup> is CH<sub>2</sub> or O;

wherein R<sup>2</sup> is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R<sup>3</sup> is O, CH<sub>2</sub> or NH.

Claim 5 (withdrawn): The method of claim 1, wherein the opioid inhibitor of the ABC drug transporter is selected from the group consisting of naltrexone, naloxone and nalmeferene.

Claim 6 (withdrawn): The method of claim 1, wherein the opioid inhibitor of the ABC drug transporter is a compound listed in Table 11.

Claim 7 (withdrawn): The method of claim 1, wherein the opioid inhibitor of the ABC drug transporter is a compound having the pharmacophore defined by:

- a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;
- a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;
- a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and
- a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

Claim 8 (withdrawn): A method of increasing efficacy of an anti-tumor agent comprising co-administering to a patient having a cancer:

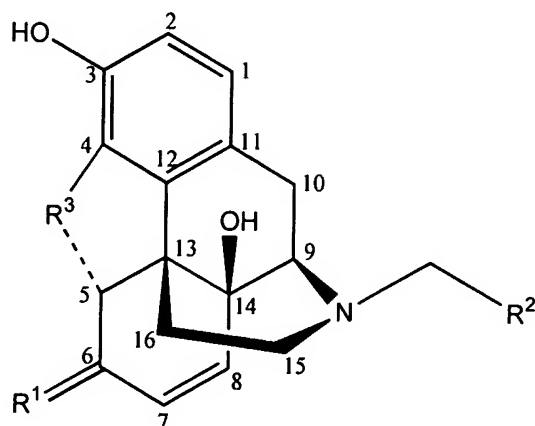
(a) a dose of the anti-tumor agent, wherein the anti-tumor agent is a substrate of an ABC drug transporter, and

(b) a dose of an opioid inhibitor of the ABC drug transporter, wherein the dose of the opioid inhibitor of the ABC drug transporter is sufficient to increase the intracellular concentration of the anti-tumor agent in a cancer cell and wherein the co-administration of the anti-tumor agent and the opioid inhibitor of the ABC drug transporter is sufficient to inhibit growth of the cancer.

Claim 9 (withdrawn): The method of claim 8, wherein the dose of the anti-tumor agent is a sub-therapeutic dose.

Claim 10 (withdrawn): The method of claim 8, wherein the anti-tumor agent is selected from the group consisting of Alkylating Agents, Antimetabolites, Vinca alkaloids, taxanes, epipodophyllotoxins, Anthracyclines, Antiproliferative agents, Tubulin Binding agents, Eneidyne, anthracededione, substituted urea, methylhydrazine derivatives, the Pteridine family of drugs, Taxanes, , Dolastatins, Topoisomerase inhibitors, Mytansinoids, and Platinum coordination complexes.

Claim 11 (withdrawn): The method of claim 8, wherein the opioid inhibitor of the ABC drug transporter is a compound of the formula:



wherein R<sup>1</sup> is CH<sub>2</sub> or O;

wherein R<sup>2</sup> is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R<sup>3</sup> is O, CH<sub>2</sub> or NH.

Claim 12 (withdrawn): The method of claim 8, wherein the opioid inhibitor of the ABC drug transporter is selected from the group consisting of naltrexone, naloxone and nalmeferene.

Claim 13 (withdrawn): The method of claim 8, wherein the opioid inhibitor of the ABC drug transporter is a compound listed in Table 11.

Claim 14 (withdrawn): The method of claim 8, wherein the opioid inhibitor of the ABC drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

Claim 15 (withdrawn): A method of decreasing toxicity associated with treating a cancer patient with an anti-tumor agent comprising co-administering to a patient having a cancer:

(a) a sub-therapeutic dose of the anti-tumor agent, wherein the anti-tumor agent is a substrate of an ABC drug transporter, and

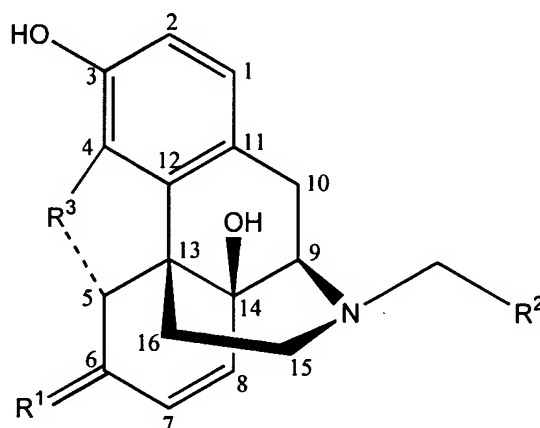
(b) a dose of an opioid inhibitor of the ABC drug transporter,

wherein the dose of the opioid inhibitor of the ABC drug transporter is sufficient to reduce efflux of the anti-tumor agent from a cancer cell and wherein the co-administration of the anti-tumor agent and the inhibitor is sufficient to inhibit growth of the cancer.

Claim 16 (withdrawn): The method of claim 15, wherein the dose of anti-tumor agent is a sub-therapeutic dose.

Claim 17 (withdrawn): The method of claim 15, wherein the anti-tumor agent is selected from the group consisting of Alkylating Agents, Antimetabolites, Vinca alkaloids, taxanes, epipodophyllotoxins, Anthracyclines, Antiproliferative agents, Tubulin Binding agents, Eneidyne, anthracededione, substituted urea, methylhydrazine derivatives, the Pteridine family of drugs, Taxanes, , Dolastatins, Topoisomerase inhibitors, Mytansinoids, and Platinum coordination complexes.

Claim 18 (withdrawn): The method of claim 15, wherein the opioid inhibitor of the ABC drug transporter is a compound of the formula:



wherein R<sup>1</sup> is CH<sub>2</sub> or O;

wherein R<sup>2</sup> is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R<sup>3</sup> is O, CH<sub>2</sub> or NH.

Claim 19 (withdrawn): The method of claim 15, wherein the opioid inhibitor of the ABC drug transporter is selected from the group consisting of naltrexone, naloxone and nalmeffene.

Claim 20 (withdrawn): The method of claim 15, wherein the opioid inhibitor of the ABC drug transporter is a compound listed in Table 11.

Claim 21 (withdrawn): The method of claim 15, wherein the opioid inhibitor of the ABC drug transporter is a compound having the pharmacophore defined by:

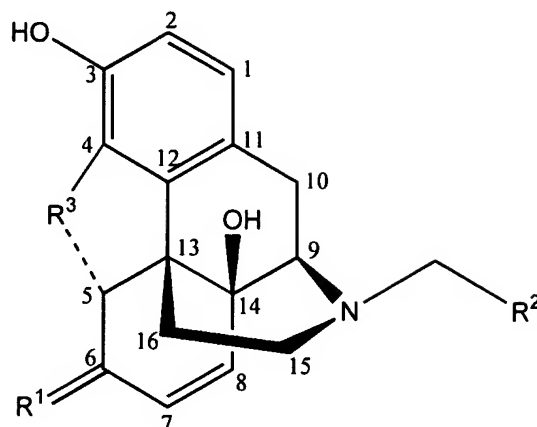
a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;  
a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;  
a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and  
a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

Claim 22 (withdrawn): A method of decreasing toxicity associated with treating a cancer patient with an anti-tumor agent comprising co-administering to a patient having a cancer:

- (a) a sub-therapeutic dose of the anti-tumor agent, wherein the anti-tumor agent is a substrate of an ABC drug transporter, and
- (b) a dose of an opioid inhibitor of the ABC drug transporter, wherein the dose of the opioid inhibitor of the ABC drug transporter is sufficient to increase the intracellular concentration of the anti-tumor agent in a cancer cell and wherein the co-administration of the anti-tumor agent and the opioid inhibitor of the ABC drug transporter is sufficient to inhibit growth of the cancer.

Claim 23 (withdrawn): The method of claim 22, wherein the anti-tumor agent is selected from the group consisting of Alkylating Agents, Antimetabolites, Vinca alkaloids, taxanes, epipodophyllotoxins, Anthracyclines, Antiproliferative agents, Tubulin Binding agents, Eneidyne, anthracenedione, substituted urea, methylhydrazine derivatives, the Pteridine family of drugs, Taxanes, , Dolastatins, Topoisomerase inhibitors, Mytansinoids, and Platinum coordination complexes.

Claim 24 (withdrawn): The method of claim 22, wherein the opioid receptor antagonist is a compound of the formula:



wherein R<sup>1</sup> is CH<sub>2</sub> or O;

wherein R<sup>2</sup> is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R<sup>3</sup> is O, CH<sub>2</sub> or NH.

Claim 25 (withdrawn): The method of claim 22, wherein the opioid inhibitor of the ABC drug transporter is selected from the group consisting of naltrexone, naloxone and nalmeferene.

Claim 26 (withdrawn): The method of claim 22, wherein the opioid inhibitor of the drug transporter is a compound listed in Table 11.

Claim 27 (withdrawn): The method of claim 22, wherein the opioid inhibitor of the drug transporter is a compound having the pharmacophore defined by:

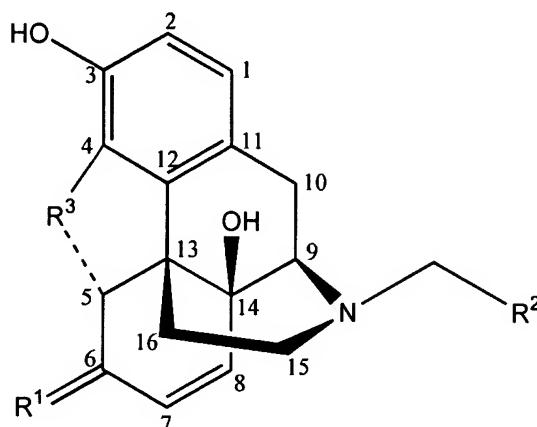
- a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;
- a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;
- a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and
- a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

Claim 28 (currently amended): A composition for treating multidrug resistant cancer cells comprising:

(a) an anti-tumor agent, wherein the anti-tumor agent is a substrate of an ABC drug transporter protein; and

(b) an ABC drug transporter protein-inhibiting amount of an opioid inhibitor of the ABC transporter protein, wherein the amount is in the range of from 0.0001  $\mu$ M to 100  $\mu$ M.

Claim 29 (original): The composition of claim 28, wherein the opioid receptor antagonist is a compound of the formula:



wherein R<sup>1</sup> is CH<sub>2</sub> or O;

wherein R<sup>2</sup> is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R<sup>3</sup> is O, CH<sub>2</sub> or NH.

Claim 30 (original): The composition of claim 28, wherein the opioid inhibitor of the ABC drug transporter is selected from the group consisting of naltrexone, naloxone and nalmeferene.

Claim 31 (currently amended): The composition of claim 28, wherein the opioid inhibitor of the drug transporter is a compound listed in Table 11 and Figs 4A-4AH.

Claim 32 (original): The composition of claim 28, wherein the opioid inhibitor of the drug transporter is a compound having the pharmacophore defined by:



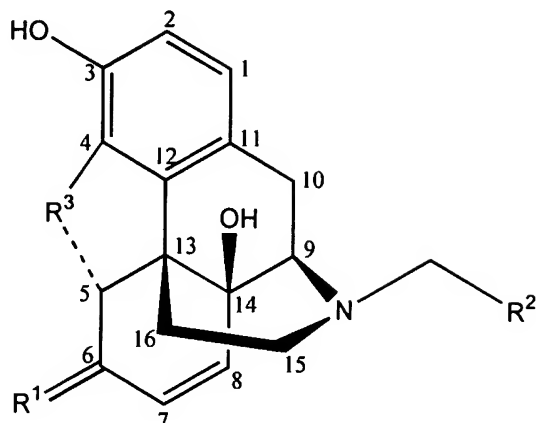
a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;  
a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;  
a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and  
a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

Claim 33 (currently amended): The composition of claim 28, wherein the anti-tumor agent is selected from the group consisting of Alkylating Agents, Antimetabolites, Vinca alkaloids, taxanes, epipodophyllotoxins, Anthracyclines, Antiproliferative agents, Tubulin Binding agents, Eneidyne, anthracenedione, substituted urea, methylhydrazine derivatives, the Pteridine family of drugs, Taxanes, [.]Dolastatins, Topoisomerase inhibitors, Mytansinoids, and Platinum coordination complexes.

Claim 34 (withdrawn): A method of enhancing the anti-tumor activity of an anti-tumor agent against a multidrug resistant cancer cell comprising:

contacting the cancer cell with the anti-tumor agent and an opioid inhibitor of an ABC drug transporter in an amount effective to inhibit a drug transporter in the cancer cell.

Claim 35 (withdrawn): The method of claim 34, wherein the opioid receptor antagonist is a compound of the formula:



wherein R<sup>1</sup> is CH<sub>2</sub> or O;

wherein R<sup>2</sup> is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R<sup>3</sup> is O, CH<sub>2</sub> or NH.

Claim 36 (withdrawn): The method of claim 34 wherein the opioid inhibitor of the ABC drug transporter is selected from the group consisting of naltrexone, naloxone and nalmeffene.

Claim 37 (withdrawn): The method of claim 34, wherein the opioid inhibitor of the drug transporter is a compound listed in Table 11.

Claim 38 (withdrawn): The method of claim 34, wherein the opioid inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

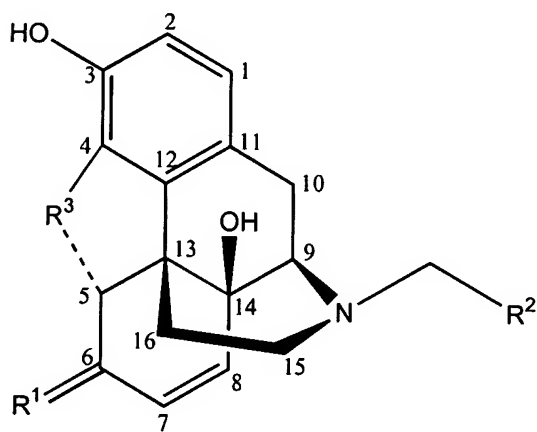
a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

Claim 39 (withdrawn): The method of claim 34, wherein the anti-tumor agent is selected from the group consisting of Alkylating Agents, Antimetabolites, Vinca alkaloids, taxanes, epipodophyllotoxins, Anthracyclines, Antiproliferative agents, Tubulin Binding agents, Eneidyne, anthracededione, substituted urea, methylhydrazine derivatives, the Pteridine family of drugs, Taxanes, , Dolastatins, Topoisomerase inhibitors, Mytansinoids, and Platinum coordination complexes.

Claim 40 (withdrawn): A method of suppressing growth of a multidrug resistant cancer cell comprising:

contacting the cancer cell with a sub-therapeutic amount of an anti-tumor agent in the presence of an opioid inhibitor of an ABC drug transporter.

Claim 41 (withdrawn): The method of claim 40, wherein the opioid inhibitor of the drug transporter is a compound of the formula:



wherein R<sup>1</sup> is CH<sub>2</sub> or O;

wherein R<sup>2</sup> is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R<sup>3</sup> is O, CH<sub>2</sub> or NH.

Claim 42 (withdrawn): The method of claim 40 wherein the opioid inhibitor of the ABC drug transporter is selected from the group consisting of naltrexone, naloxone and nalmeffene.

Claim 43 (withdrawn): The method of claim 40, wherein the opioid inhibitor of the drug transporter is a compound listed in Table 11.

Claim 44 (withdrawn): The method of claim 40, wherein the opioid inhibitor of the drug transporter is a compound having the pharmacophore defined by:

- a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;
- a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;
- a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and
- a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

Claim 45 (withdrawn): The method of claim 40, wherein the anti-tumor agent is selected from the group consisting of Alkylating Agents, Antimetabolites, Vinca alkaloids, taxanes, epipodophyllotoxins, Anthracyclines, Antiproliferative agents, Tubulin Binding agents, Eneidiynes, anthracededione, substituted urea, methylhydrazine derivatives, the Pteridine family of drugs, Taxanes, , Dolastatins, Topoisomerase inhibitors, Mytansinoids, and Platinum coordination complexes.

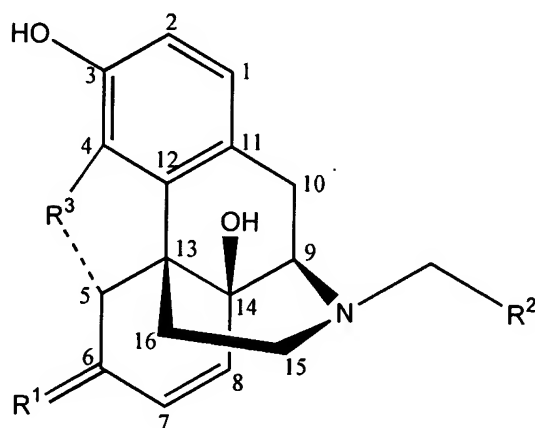
Claim 46 (withdrawn): A method of inhibiting a P-glycoprotein in a patient suffering from cancer comprising administering to the patient a P-glycoprotein inhibiting amount of an inhibitor of an ABC drug transporter, wherein the inhibitor is selected from the group consisting of naltrexone, naloxone and nalmefene,

wherein the inhibitor is administered before, with, or after the administration to the patient of a therapeutic or sub-therapeutic amount of an anti-tumor agent.

Claim 47 (withdrawn): The method of claim 46, wherein the P-glycoprotein is PGP1a.

Claim 48 (withdrawn): The method of claim 46, wherein the anti-tumor agent is selected from the group consisting of Alkylating Agents, Antimetabolites, Vinca alkaloids, taxanes, epipodophyllotoxins, Anthracyclines, Antiproliferative agents, Tubulin Binding agents, Enediynes, anthracededione, substituted urea, methylhydrazine derivatives, the Pteridine family of drugs, Taxanes, , Dolastatins, Topoisomerase inhibitors, Mytansinoids, and Platinum coordination complexes.

Claim 49 (withdrawn): A method of inhibiting a P-glycoprotein in a patient suffering from cancer comprising administering to the patient a P-glycoprotein inhibiting amount of an inhibitor of an ABC drug transporter, wherein the inhibitor of the ABC drug transporter is a compound of the formula:



wherein R<sup>1</sup> is CH<sub>2</sub> or O;

wherein R<sup>2</sup> is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R<sup>3</sup> is O, CH<sub>2</sub> or NH,

wherein the inhibitor is administered before, with, or after the administration to the patient of a therapeutic or sub-therapeutic amount of an anti-tumor agent.

Claim 50 (withdrawn): The method of claim 49, wherein the P-glycoprotein is PGP1a.

Claim 51 (withdrawn): The method of claim 49, wherein the anti-tumor agent is selected from the group consisting of Alkylating Agents, Antimetabolites, Vinca

alkaloids, taxanes, epipodophyllotoxins, Anthracyclines, Antiproliferative agents, Tubulin Binding agents, Enediynes, anthracededione, substituted urea, methylhydrazine derivatives, the Pteridine family of drugs, Taxanes, , Dolastatins, Topoisomerase inhibitors, Mytansinoids, and Platinum coordination complexes.

Claim 52 (withdrawn): A method of identifying a compound for improved treatment of multidrug resistant cancers comprising:

- (a) identifying an anti-tumor agent;
- (b) assaying the ability of the anti-tumor agent to be transported across a membrane by an ABC protein; and
- (c) repeating the transport assay to determine whether addition of an opioid receptor antagonist inhibits transport of the anti-tumor agent across the membrane, whereby the compound which is active in the brain, is transported by an ABC protein and whose ABC protein-mediated transport is inhibited by the opioid receptor antagonist is identified.

Claim 53 (withdrawn): The method of claim 52, wherein the opioid receptor antagonist is nalmefene, naloxone, or naltrexone.

Claim 54 (withdrawn): A method of enhancing the potency of a compound identified by the method of claim 52 comprising:

co-administering a therapeutic amount of the compound and an amount of an opioid receptor antagonist capable of inhibiting a drug transporter, wherein the amount of the opioid receptor antagonist is sufficient to reduce transport of the compound across a biological membrane.

Claim 55 (withdrawn): A method for screening for an opioid inhibitor of an ABC drug transporter, comprising determining whether a potential opioid inhibitor inhibits growth of a cancer cell in the presence of sub-therapeutic amount of anti-tumor agent, wherein the cancer cell expresses an ABC drug transporter, and wherein said determining comprises comparing the growth of the cancer cell which expresses the ABC drug transporter, with growth of a second cancer cell which

does not produce the ABC drug transporter, wherein the first and second cancer cells are grown in the presence of the sub-therapeutic amount of the anti-tumor agent.

Claim 56 (withdrawn): A method for screening for an opioid inhibitor of an ABC drug transporter, comprising:

contacting a potential opioid inhibitor of an ABC drug transporter protein with the ABC drug transporter protein in the presence of a compound selected from the group consisting of naltrexone, naloxone and nalmefene, wherein the compound is detectably labeled;

measuring the amount of detectably labeled compound bound to the ABC drug transporter; and

comparing the measured amount to the amount of detectably labeled compound bound by the ABC drug transporter when the drug transporter is contacted with the compound alone,

whereby a measured amount lower than the amount of compound bound to the ABC drug transporter when contacted alone identifies an opioid inhibitor of the ABC drug transporter.

Claim 57 (withdrawn): The method of claim 56, wherein the potential opioid inhibitor of the ABC drug transporter is selected from the compounds listed in Table 11.

Claim 58 (withdrawn): A method of treating a cancer in an animal, comprising administering to the animal suffering from the cancer an anti-tumor agent and an ABC drug transporter inhibitor in an amount sufficient to increase the intracellular concentration of the anti-tumor agent in a cancer cell,

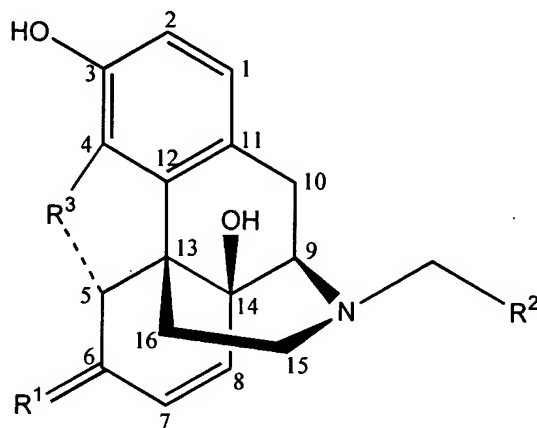
wherein the ABC drug transporter inhibitor increases the susceptibility of the cancer to the anti-tumor agent, and

wherein the ABC drug transporter inhibitor is selected from the group consisting of naltrexone, naloxone and nalmefene.

Claim 59 (withdrawn): A method of treating a cancer in an animal, comprising administering to the animal suffering from the cancer an anti-tumor agent and an ABC drug transporter inhibitor in an amount sufficient to increase the intracellular concentration of the anti-tumor agent in a cancer cell,

wherein the ABC drug transporter inhibitor increases the susceptibility of the cancer cell to the anti-tumor agent, and

wherein the ABC drug transporter inhibitor is a compound of the formula:



wherein R<sup>1</sup> is CH<sub>2</sub> or O;

wherein R<sup>2</sup> is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R<sup>3</sup> is O, CH<sub>2</sub> or NH.